Editorials

How About Some Affirmative Action for Patient Advocacy?

PATIENT ADVOCACY appears to be a logical extension of a doctor's professional commitment to do what he or she believes best for his or her patient. In simpler times little more was involved than the professional relationship between the two. Perhaps a nurse or a local hospital might be involved. But the times are no longer simple. Health care has become a complex system, embodying many forces that profoundly affect patient care. Each of these forces (we call them third parties) has its own interests and objectives within the health care system, and these may or may not be in the best interests of patients, either individually or collectively. So far there has been no clearly identified advocate of patients' interests in this complex system that has developed so many new dimensions. This was recognized some time ago by the leaders of organized medicine who proclaimed, with some fanfare, that physicians and the medical profession should assume the role of advocates of patients wherever this might be needed in health care. This call to action was repeated in many medical forums throughout the country. But there is too little evidence that much has happened. There has been surprisingly little discussion of just what is the meaning of patient advocacy, or just what are the responsibilities and duties of individual physicians and organized medicine as patient advocates in today's health care environment.

When one thinks about it, the role of patient advocacy for physicians and organized medicine could be a sleeping social, economic and political giant. After all, patients are what health care, and therefore the health care system, are all about. The public easily identifies with patients and may be expected to identify easily with whomever it believes to be genuine patient advocates. But here there seems to be sort of a slip twixt the cup and the lip. The public does not yet identify organized medicine, or even physicians, with patient advocacy within the health care system. Self-proclaimed advocacy has not been enough. Rather there are suspicions that some physicians may become increasingly self serving under the economic pressures of the new health care environment, while organized medicine continues to be too often perceived as more of a trade association whose foremost purpose is to protect the economic interests of physicians. It seems obvious that unless something fairly convincing, perhaps even dramatic, is done to change these perceptions, this potentially very important and helpful political giant will remain asleep.

What to do? Patient advocacy by individual physicians and organized medicine must somehow become a genuine commitment with recognized good performance that is highly visible for all to see. It should be reaffirmed over and over again that a physician's first duty is to a patient, and particularly a sick patient, no matter what the health care arrangements or what the social, economic or political interests of the physician may be. This should be visible for all to see, even in the media when appropriate. In the social arena, there are many patients and potential patients whose health care needs are not now being effectively advocated by anyone while they seem to be falling relatively unnoticed through the cracks in the current competitive health care system. Perhaps organized medicine could create a data base for patient access to care, much as it now has an authoritative and respected data base for the qualifications and practice of physicians, whether or not they belong to the AMA. In the economic sphere there is much that physicians and organized medicine could do by bringing their scientific and experiential expertise to bear to reduce waste and unnecessary expense to patients, and in politics some lessons might be learned from an organization such as the American Association of Retired Persons (AARP), which has succeeded in becoming a recognized and effective social, economic and political advocate of the interests of another very large segment of the population, the elderly.

But so far not very much seems to be happening—or if it is, it is not very visible or being recognized as genuine activist patient advocacy by physicians and the medical profession. And the public has yet to be impressed, let alone convinced. The great giant sleeps relatively undisturbed, and will likely continue to do so unless there is aggressive, and perhaps even massive *affirmative action* on the part of physicians and organized medicine to make the profession's patient advocacy an effective day-to-day reality visible for all to see. The giant is there, and sooner or later someone will surely awaken it. And on the bleak side, it has been suggested with some authority that at the present moment much of the public may hold the perception that the government is more on their side and acting more in their behalf in health care than is organized medicine.

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Those Nasty Radicals

THE DIVERSITY of clinical conditions in which there is evidence for the role of oxygen-derived free radicals is outlined in broad brush strokes in this issue by Katz. What is remarkable about oxygen radicals is their apparent role in a variety of pathological conditions such as ischemia, immunological disorders, trauma, dietary deficiency states, radiation injury and aging, to name just a few. Thus, oxygen radicals seem to have roles in disease processes in which there is little apparent commonality of causation.

The source of oxygen radicals in biological systems is a function of enzyme pathways that initiate transfer of *single* electrons, thus producing, by definition, chemical radicals which contain in the outer electron orbit an unpaired electron. Oxygen radicals tend to be highly unstable and will either give up or take on an electron to gain parity. Accordingly, radicals can act as either reducing or oxidizing agents. The electron transport systems such as those contained in mitochondria are, by and large, efficient in the simultaneous transfer of two electrons, virtually excluding the formation of oxygen radicals. On the other hand, the electron transport system on the cell membrane of phagocytic cells (macrophages, mono-

cytes, neutrophils, eosinophils) contains the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, which is designed to transfer single electrons to oxygen.[1] The product is always an oxygen radical, superoxide anion ($O_2^{-\bullet}$), and its subsequent successive electron reduction products, which include H_2O_2 (hydrogen peroxide) and the hydroxyl radical ($HO^\bullet$). While $HO^\bullet$ appears to be the most unstable and reactive of the oxygen radicals, phagocytic cells can also convert H_2O_2 in the presence of myeloperoxidase and halide to other noxious agents such as hypochlorous acid and stable chloramines, all of which are potent oxidants.

Within phagocytic cells, in addition to the NADPH-oxidase system, it is possible to derive oxygen radicals from other electron transport pathways, including those contained in mitochondria, microsomes, peroxisomes and the cyclooxygenase pathway in the arachidonic acid cascade. Under most situations, however, it is the NADPH-oxidase pathway that is far and away the most important source of oxygen radicals in phagocytic cells. This pathway exists for the purpose of killing microbes that undergo phagocytic ingestion. The NADPH-oxidase system can also be readily triggered by surface-related events—such as contact of phagocytic cells with chemotactic peptides or immune complexes—in which the activated region of the cell membrane remains on the external surface of the phagocyte, rather than being internalized and incorporated into a phagocytic vacuole where oxygen radicals can be sequestrated from both the cell and the extracellular environment. When the activated segment of cell membrane remains on the cell surface and is not internalized, oxygen radicals have nowhere to go but to diffuse away from the phagocyte, striking whatever happens to be in the path, be these cells, basement membrane, connective tissue matrix, proteins in interstitial fluids and the like. These circumstances appear to be relevant to tissue damage associated with a variety of inflammatory conditions in which either residential or recruited blood phagocytic cells are activated to produce oxygen radicals.[2]

As Katz also emphasizes, another source of oxygen radicals is the xanthine oxidase system, which exists in most cells throughout the body, with the possible exception of the central nervous system. This enzyme can be activated by the release of proteases within lysosomal granules contained within cells. McCord and colleagues have developed the concept that xanthine oxidase is responsible for the ultimate, fully expressed tissue damage accompanying ischemic injury of the small bowel or myocardium.[3] If xanthine oxidase is important in ischemic injury, as the case seems to be, details of the pathophysiologic events are unclear. Is $O_2^{-\bullet}$ generated exclusively intracellularly and, if so, are all of the pathogenic events also intracellular? If this is the case, injury by the xanthine oxidase system would appear to be entirely limited to individual cells in which xanthine oxidase has been activated. That intervention in ischemic injury with the enzyme superoxide dismutase (by its conversion of $O_2^{-\bullet}$ to H_2O_2) protects against ischemic injury of the bowel or myocardium suggests that $O_2^{-\bullet}$ (or its derivatives) must be exiting from the cell of origin because it is unlikely that superoxide dismutase can gain entry to the intracellular environment. Working out these details is important because the development of effective protective interventions will probably rely on some of this information. The role of the xanthine oxidase system stands in sharp contrast to the NADPH-oxidase system in phagocytic cells in which the injury to target cells appears to proceed not from within the target cell but from the effector cell, with bombardment of the target cell from the exterior. The attractiveness of the xanthine oxidase hypothesis is the susceptibility of the enzyme to inhibition by allopurinol. In view of conflicting evidence for the origin of oxygen radicals involved in ischemic damage of the myocardium (xanthine oxidase versus neutrophil-associated NADPH oxidase),[4,5] more work needs to be done to clarify the picture. There is intriguing but unconfirmed evidence suggesting that ischemic injury of the central nervous system may also be related to a role for oxygen radicals.

Oxygen radicals bring about damage by a variety of mechanisms, both direct and indirect, and these reactions can involve intact cells, intracellular components and connective tissue matrices, to name just a few targets. Cross-linking or peroxidative changes in proteins or glycosaminoglycans, peroxidation of lipids with scission and release of aldehydes, oxidative inactivation of protease inhibitors, oxidative changes resulting in strand breaks in DNA or sister chromatid exchanges are only a few of the chemical reactions or events ascribed to the effects of oxygen radicals.[1] What is apparent is that the outcome of these chemical reactions can be expressed in a variety of ways, ranging from cell dysfunction and potential mutagenesis to outright cell necrosis.

Emerging from many laboratories is evidence that iron plays an important role in oxygen radical-mediated tissue damage. Although it has been known for some time that the addition of iron in the presence of lipid results in peroxidation and it has been many years since Fenton described the ability of iron to catalyze the transfer of an electron from $O_2^{-\bullet}$ to H_2O_2, resulting in the appearance of $HO^\bullet$, only recently has the key role of iron been appreciated in oxygen radical-mediated events in vivo.[6-9] Experimental immune complex injury of vessels and complement and neutrophil-dependent (and oxygen radical-mediated) damage of endothelial cells in vivo can be blocked by the application of iron chelators. Thus, it appears that irrespective of whether $O_2^{-\bullet}$ is being formed by xanthine oxidase or by NADPH oxidase, its conversion to H_2O_2 and the iron catalyzed reduction of H_2O_2 to $HO^\bullet$ are key events leading to tissue injury. From these observations derive the various therapeutic strategies that have been successfully used in experimental animals: antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase/reductase), relatively specific (dimethyl sulfoxide) or nonspecific (vitamin E) scavengers, inhibition of xanthine oxidase (allopurinol) or its product, $O_2^{-\bullet}$ (superoxide dismutase) and iron chelators (apolactoferrin, deferoxamine). To what extent these agents will have applicability in human diseases or syndromes remains to be determined. Although these interventions have the potential to interfere with the normal oxygen-dependent antimicrobial mechanisms of phagocytic cells, it seems likely that the cautious use and "clinical titration" of the drugs will probably circumvent these potential problems, much as is the case with the clinical use of immunosuppressive drugs.

It should not be a terribly time-consuming process to determine if some of these interventions will be clinically useful. In the case of the adult respiratory distress syndrome in which there is evidence for oxygen radical-mediated events, given

the 50% lethality of these patients over a 72-hour period, the utility of these potential therapeutic interventions should be quite amenable to analysis. Other conditions such as those of ischemia could pose formidable problems in determining whether or not antioxidant interventions will be useful. Obviously, reliable guideposts such as a dramatically lowered incidence of postmyocardial infarct arrhythmias, obvious clinical salvage in acute spinal cord injuries and the like would be the types of determinants that would need to be carefully selected and agreed upon before clinical trials.

The great breadth and diversity of clinical conditions in which oxygen radicals may be involved in the pathogenesis of tissue damage should be of interest to all clinicians. It can be predicted that, as our knowledge and understanding of oxygen radical mechanisms improve, we will likely see the emergence of a new pharmacologic approach to the development of anti-inflammatory therapy.

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Of English and Health Care

ELSEWHERE IN this issue is a study by Hu and Covell indicating that health care usage among Hispanic patients correlates positively with their ability to communicate in English. The study was done in five outpatient clinics in San Diego County in California, an area in which the population is heavily Hispanic and where all of the clinics had bilingual personnel. One might surmise that if a working knowledge of English is important for adequate participation in the health care that is available in America, it is probably also important for adequate participation in many other aspects of American life.

In many parts of the country there are large and growing populations that speak little or no English. This is not only a problem in health care, but it is also a problem of particular and often critical importance in many of the nation's schools. Understandably in an egalitarian society, there is great emphasis on providing bilingual or multilingual health care workers, teachers and classroom instruction, and in some places providing ballots and voting information in several languages. All of these are commendable and even necessary activities to help non-English-speaking persons to move more nearly into the mainstream of American life. But is this really enough? Is it really enough to recognize the equal rights of separate cultures and separate languages to coexist within the social, economic and political framework of America? Ought we not to ask whether these persons of separate cultures and separate languages can ever fully participate in or contribute to the American way of life without mastery of the nation's common language of communication, which is English? Probably they cannot. After all, our laws are in English, our business is conducted in English and our way of life is communicated at home and abroad in English. And it may well be that those who have come to America, seeking to enjoy its benefits for themselves and their children, will begin to realize their goal of full participation only as soon as they can make the English language their own.

The positive correlation of an ability to communicate in English with an optimal use of the health care system demonstrated by the study in San Diego County may be a simple observation, but one that could have profound significance. If so, then, in our quest for an egalitarian society, we should be careful not to lose sight of the incentives and genuine need for mastery of English as an essential ingredient of full participation in an America that continues to welcome immigrants to its shores and across its borders.

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